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| 09/410,336 | 10/01/1999 | SUSAN LOVE | 18612-000410 | 6727 |

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BANNER & WITCOFF, Ltd.
1001 G Street, N.W. Eleventh Floor
Washington, DC 20001-4597

| EXAMINER | |
|---|---|
| RAWLINGS, STEPHEN L | |

| ART UNIT | PAPER NUMBER |
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| 1642 | 17 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/410,336 | LOVE ET AL. | |
| | Examiner | Art Unit | |
| | Stephen L. Rawlings, Ph.D. | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 September 2001 and 04 December 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *17-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-32* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. The amendment filed December 4, 2001 in Paper No. 16 is acknowledged and has been entered. Claims 1, 5, 9, and 13 have been amended.

2. Claims 1-32 are pending in the application. Claims 17-32 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

3. Claims 1-16 are currently under prosecution.

### *Claim Rejections Withdrawn*

4. In the Office Action mailed March 9, 2001 (Paper No. 9), claims 1-16 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth in section 6 of the Office Action. In reply to the Office Action, Applicants have amended claims 1, 5, 9, and 13, thus obviating the grounds of the rejection. Therefore, the rejection of claims 1-16 under 35 USC § 112, second paragraph for the reasons stated in section 6 of the Office Action mailed March 9, 2001 is withdrawn.

### *Claim Rejections Maintained and Answer to Applicants' Remarks*

***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 9-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons stated in section 4 of the Office Action mailed March 9, 2001.

The claims are drawn to a method of determining the lymph node involvement in patients diagnosed with premalignant or malignant breast cancer growths, said method comprising delivering an identifying agent, which can be coupled to a targeting molecule, through one or more preselected breast ducts in amount sufficient to detect lymph node involvement by a procedure that involves cannulation or catheterization of the breast duct(s) and wherein detecting lymph node involvement can comprise detecting the agent in a sentinel lymph node. The specification teaches a method of identifying the location of premalignant or malignant breast cancer cells within the breast duct or breast ductal network of a patient, said method comprising delivering an identifying agent, which can be coupled to a targeting molecule, through one or more breast ducts by a procedure that involves cannulation or catheterization of the breast duct(s) (see Examples 1 and 2, pages 16-18). The specification also discloses that "the invention provides novel methods for staging a neoplastic breast lesion and a means to identify peripheral (sentinel) lymph node involvement" and "lymph node involvement includes sentinel node involvement" (page 6, lines 24-26). However, the specification does not teach how the determination of lymph node involvement can be made after delivering an identifying agent through a cannula or catheter into the lumen of one or more breast ducts. The teachings of the specification cannot be extrapolated to the enablement of the claims because the specification does not teach a method of determining the lymph node involvement in patients diagnosed with premalignant or malignant breast cancer growths. Because there is insufficient guidance in the specification that would enable one of skill in the art to practice the claimed invention and thereby make the determination that there is lymph node involvement in a patient with a reasonable expectation of success without need to perform undue experimentation, the disclosure fails the meet the enablement requirement of 35 USC § 112, first paragraph.

The reasons that the disclosure fails the meet the enablement requirement of 35 USC § 112, first paragraph, which were stated in the Office Action, include:

(1) The specification does not define "lymph node involvement". In general, lymph node involvement in a patient diagnosed with breast cancer refers a case in which metastatic cells have been identified in the local or axillary lymph nodes.

(2) The specification does not teach how, or by what criteria, the detection of an identifying agent in a sentinel lymph node is a determinant of lymph node involvement.

Certainly, the mere presence of the identifying agent in a sentinel lymph node is not the sole criterion for determination of lymph node involvement. Since the sentinel node is the first node in the lymphatic system to receive drainage from a tumor, it would be expected that some dye, contrast agent, or radioactive tracer injected into the lumen of a breast duct *via* the catheter would flow over into the sentinel lymph node; however, the presence of this over-flow would not be indicative of lymph node involvement, *per se*.

(3) There are no working examples that might illustrate to one of skill in the art how the claimed invention can be used to determine whether there is lymph node involvement in a patient diagnosed with breast cancer.

(4) Neither the claims nor the specification teach that biopsied samples of lymph nodes are to be collected and/or that histopathologic analysis should be performed in conjunction with the claimed method steps; yet histopathologic analysis of cells biopsied from the lymph nodes is the most common method by which one of skill in the art would determine if there were lymph nodes involved. In fact, Krag, et al suggest that since the sentinel node is the first stop along the route of lymphatic drainage from a primary tumor, histopathological examination of the sentinel node should be conducted before more extensive lymphadenectomy is performed. It seems therefore, in the absence of histopathologic examination of the excised tissue surrounding and including the cells of the sentinel lymph node confirming the presence of malignant cells, the claimed invention could not be used to determine whether lymph node involvement has occurred, since even if an identifying agent was coupled to a targeting molecule, such as an antibody that specifically binds a marker on cancerous cells, was used in practicing the claimed method, one of skill in the art cannot predict the effectiveness of the claimed method to enable a determination of lymph node involvement in a patient.

(5) There is insufficient guidance in the specification to enable one to practice the method with a reasonable expectation of success without need to perform undue experimentation. As evidence of the insufficiency of the disclosure, it was noted that there is no guidance either in the claims or the specification that would enable one to distinguish specific from non-specific labeling of cells to which the targeting molecule may interact. Also, there is also no step in the claimed method in which unbound, excess identifying agent coupled to a targeting molecule is washed from the lymph node; therefore, the identifying agent will be detected in the lymph node

regardless of whether there are malignant cells present, leading to an unpredictability and an inaccuracy in making the determination that there is or is not lymph node involvement.

In reply to the Office Action mailed March 9, 2001 Applicants traverse the rejection of claims 9-16 under 35 USC § 112, first paragraph arguing that the present invention relates to in vivo determinations of the presence of cancerous or precancerous cells by identifying *only* the location of a cancerous or precancerous cell in the breast duct or breast ductal network. Applicants further state, "the methods according to the present invention do not identify the remainder of the breast duct or the sentinel lymph nodes". Applicants assert that the invention eliminates the need for invasively obtaining cells in order to determine if the cells in question are cancerous or precancerous and/or if a lesion is present.

In response to Applicants' argument, the claims are drawn to a method for determining whether the lymph nodes are involved in patients diagnosed with premalignant or malignant breast cancer growths. Therefore, contrary to Applicants' arguments, the present invention does not relate to *in vivo* determinations of the presence of cancerous or precancerous cells by identifying *only* the location of a cancerous or precancerous cell in the breast duct or breast ductal network. Instead, presumably since the claims recite that the patients have been diagnosed with premalignant or malignant breast cancer growths, the location of the cancerous or precancerous cells in the breast duct or breast ductal network is already known and according to the claims, the objective of the method is to determine if the lymph nodes have become involved in the disease. The remainder of Applicants' argument is moot.

Applicants' argument has been carefully considered but not found persuasive; therefore, the rejection of claims 9-16 under 35 USC § 112, first paragraph for the reason stated in section 4 of the Office Action mailed March 9, 2001 is maintained.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete because claims 1, 5, 9 and 13 omit one or more essential steps, such omission amounting to a gap between the steps for the reasons stated in the previous Office Action.

As stated in the Office Action mailed March 9, 2001, the omitted steps in claims 1, 5, 9, and 13 are: (a) a step in which the identifying agent or targeting molecule coupled to an identifying agent is detected and (b) a step in which the data acquired in the detection step are correlated with the anatomy of the breast to assign a location to the premalignant or malignant breast cancer within a duct or ductal network (claims 1-8) or a step in which the data acquired in the detection step are correlated with the anatomy of the axillary lymph nodes to determine whether there is lymph node involvement in the patient. It is noted that claims 10 and 14 recite a step in which the agent is detected; however, claims 10 and 14 are still indefinite because of the omission of a step in which the data acquired in the detection step are correlated with the anatomy of the axillary lymph nodes to determine whether there is lymph node involvement in the patient.

In reply to the Office Action, Applicants traverse the rejection arguing that the steps in question are not essential. Applicants argue that it is not necessary to recite steps in the claimed methods that are not described as being essential in the specification. In response to Applicants' argument, MPEP § 2172.01 states, "[a] claim omits matter disclosed to be essential to the invention as described in the specification or in other statements of record". The specification discloses in the first example (page 16, line 31 – page 17, line 1): "An MRI is conducted on the animals to determine the location of breast cancer lesions inside the breast ducts. Information of lesion location correlated between the MRI, repeated mammograms and physical examinations". In the second example, the specification discloses (page 29, lines 29-31): "An MRI is conducted on the animals to determine the location of breast cancer cells inside their breast ducts. The correlation of tumor location is determined between the MRI and repeated physical examination mammogram". Thus, since the only exemplification of the claimed methods taught in the specification includes a disclosure that the method involves detecting the identifying agent or targeting agent coupled to an identifying agent by MRI would suggest, contrary to Applicants' assertion, that a step in which the identifying agent or targeting agent coupled to an identifying agent is detected is an essential step. Similarly, since the only exemplification of the claimed methods taught in the specification includes a disclosure that the method involves correlating the anatomy of the breast during repeated physical examinations and mammograms and the data acquired by MRI would suggest, also contrary to Applicants' assertion, that a step in which the

data acquired in the detection step are correlated with the anatomy of the breast to assign a location to the premalignant or malignant breast cancer within a duct or ductal network is an essential step. MPEP § 2172,01 also states, "[i]n addition, a claim which fails to interrelate essential elements of the invention as defined by applicant(s) in the specification may be rejected under 35 USC § 112, second paragraph, for failure to point out and distinctly claim the invention". Since Applicants have acknowledged that a claim must recite steps in the claimed methods that are described as being essential in the specification, it is fair to presume that the steps included in the claims are in fact essential. Then, since the steps recited in the claims are essential, if the claims fail to recite a step that interrelates the essential elements (i.e., steps) of the invention, it is correct to reject the claims under 35 USC § 112, second paragraph as failing to point out and distinctly claim the invention. The claims currently recite, for example, the steps of providing a targeting molecule coupled to an identifying agent, delivering the coupled compound, and identifying the location of the cancer within the breast duct. Notably the claims fail to recite a step or steps that interrelates the element of the invention in which the coupled compound is delivered and the element of the invention in which the location of the cancer within the breast duct is identified. In other words, the claims fail to recite an essential step, such omission amounting to a gap between the steps. Also, logically, it is not apparent why Applicants contend that the steps, which the Examiner finds missing, are not essential, since Applicants have not described a method that does not comprise such steps and have not provided any factual evidence that such steps are not essential. For these reasons, Applicants arguments, although carefully considered, have not been found persuasive and the rejection of claims 1-16 under 35 USC § 112, second paragraph for the reasons stated in section 7 of the Office Action mailed March 9, 2001 is maintained.

### *Claim Rejections - 35 USC § 102*

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 5-8 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Hou, et al (*Radiology* **195**: 568-569, 1995; Form PTO-1449 (Paper No. 7), citation AR), as evidenced by Van Zee, et al (*Cancer* **82**: 1874-1880, 1998; Form PTO-1449 (Paper No. 7), citation BA) for the reason stated in the previous Office Action.

In response to the Office Action mailed March 9, 2001, Applicants traverse this rejection of the claims under 35 USC § 102(b) arguing that methylene blue is not a "cancer specific agent" as recited in the present claims and therefore the step of introducing methylene blue into the breast duct does not anticipate the step of "providing a premalignant or malignant cancer cell specific identifying agent".

In reply to Applicants' arguments, the term "cancer cell specific identifying agent" does not appear to be defined in the specification. The American Heritage® Dictionary of the English Language: Fourth Edition, 2000, defines "specific" as "[r]elating to, characterizing, or distinguishing a species" (Copyright © 2000 by Houghton Mifflin Company). Thus, a "cancer specific identifying agent" in the context of the claim would be reasonably defined as an identifying agent that distinguishes breast cancer tissue from normal breast tissue. Because methylene blue differentially stains premalignant or malignant breast tissue and enables the clinician to distinguish breast cancer tissue from normal breast tissue, it would appear that methylene blue is a "cancer specific identifying agent". Also, Hou, et al teach, "the duct and any involved lobules could be identified by the presence of the blue dye" (page 568, column 3).

Furthermore, Hou, et al disclose, "[d]uct cannulation was successfully performed with our technique, which facilitated injection of contrast material for galactography and of dye for localization" (page 569, column 2). Thus, Hou, et al also teach the injection of contrast material for galactography and as noted in the Office Action, as evidenced by Van Zee, et al, "galactography allows preoperative determination of the number, location, and extent of the lesion(s)" in the breast of patients. Obviously, galactography enables the clinician to specifically identify cancer in the breast, which, of course, would then necessarily involve the use of "cancer specific identifying agents". So in this instance, the contrast material of Hou, et al is also a deemed an example of a "cancer specific identifying agent", which according to the method of Hou, et al is delivered by cannulation through a breast duct in an amount sufficient to identify premalignant or malignant cancerous cells for purpose of excising the tissue surrounding and

including the identified tissue. Since the specification exemplifies "an identifying agent" as a radiographic contrast agent (page 11, lines 7-22), it would seem that the contrast material of Hou, et al can be viewed as an acceptable identifying agent, which can be delivered by cannulation through a breast duct in an amount sufficient to identify premalignant or malignant cancerous cells for purpose of excising the tissue surrounding and including the identified tissue.

Applicants arguments have been carefully considered but not found persuasive for the reasons stated in the paragraphs above. Therefore, the rejection of claims 5-8 under 35 USC § 102(b) for the reason stated in section 9 of the Office Action mailed March 9, 2001 is maintained.

Nonetheless, for the sake of argument, even if a "cancer specific identifying agent" were to have been defined as an "identifying agent that binds exclusively to cancer cells", Applicants arguments would raise additional issues, which would have to be addressed. For example, it is noted that the specification teaches that the identifying agent can comprise a targeting agent and exemplifies a targeting agent as an antibody. The specification exemplifies an antibody as an antibody that binds specifically to ErbB2. However, an identifying agent comprising an antibody that binds specifically to ErbB2 cannot be said to be a "cancer specific identifying agent" according to this definition since the antibody does not bind exclusively to cancer cells, but also binds normal cells because normal cells also express ErbB2. The other exemplary identifying agents are also not exclusively specific for cancer. Therefore, it seems that Applicants have not disclosed an identifying agent that is "cancer specific" in the sense that it binds cancer cells but not normal cells.

### *Claim Rejections - 35 USC § 103*

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hou, et al (*Radiology* **195**: 568-569, 1995; Form PTO-1449 (Paper No. 7), citation AR) in view of Allan, et *al (British Journal of Cancer* **67**: 706-712, 1993) and Vitetta, et al (*Cancer Research* **54**: 5301-5309, 1994), as evidenced by Krag, et al (*New England Journal of Medicine* **339**: 941-946, 1998; Form PTO-1449 (Paper No. 7), citation AT) for the reason stated in the Office Action mailed March 9, 2001.

In response to the Office Action mailed March 9, 2001, Applicants traverse this rejection of the claims under 35 USC § 103(a) arguing that the proposed modification of the method of Hou with the step of substituting the agent of Allan, i.e., Allan, et al, for the agent of Hou would not have been obvious for reasons including (a) no motivation exists for the asserted combination, (b) impermissible hindsight has been used to pick and choose portions of the Allan method while ignoring others, (c) no expectation of success exists for this modification, and (d) the steps needed to prepare the agent disclosed in Allan's method contradict the method set forth in Hou.

In response to Applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In reply to Applicants' argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In reply to Applicants' argument that no teachings exist in either reference that would have lead one of ordinary skill in the art to derive the claimed invention by modifying the method of Hou in view of Allan, et al, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references.

Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

In response to Applicants' argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one would have been motivated to substitute the targeted identifying agent of Allen, et al for the identifying agent of Hou, et al because the increased specificity of the method would enable the clinician to make more accurate identification of the location of malignant breast cancer cells within the duct of a patient's breast and a more accurate determination of lymph node involvement in the patient, taking into account the teachings of Vitetta, et al and Krag, et al. Since the breast ductal network and axilla are the targeted tissues, the use of the targeting agent of Allen, et al in the method of Hou, et al would provide an enormous advantage to the clinician because cannulation of a breast duct would permit direct access to the targeted tissues, enabling a better image to be acquired without using excessive amounts of the identifying agent, and thereby enable a better and more accurate diagnosis without risking harm to the patient by delivering unnecessarily large quantities of antibodies and radioisotopes that may have adverse effects.

In response to Applicants' argument that no expectation of success exists for the modification of the method of Hou, et al in view of Allan, et al, it is noted that Applicants' have offered no reasoning or substantive evidence to support this assertion. It is not immediately apparent why the modification of the method of Hou, et al in view of Allan, et al, as proposed in the rejection, would not have successfully arrived at the invention. Contrary to Applicants' opinion, then, there does not appear to be a reason one of ordinary skill in the art would not have had a reasonable expectation of success in combining the teachings of Hou, et al and Allan, et al and more specifically modifying the method of Hou, et al to replace the identifying agent of Hou, et al with the identifying agent of Allan, et al and thereby deriving an invention such as that which is claimed in the instant application. Furthermore, both the methods of Hou, et al and

Allan, et al had demonstrated success and as stated in the Office Action, because the identifying agent of Allan, et al is coupled to a targeting molecule that enables the identifying agent to specifically target malignant breast cancer cells and because the method of Hou, et al enables one to deliver the agent directly to the targeted site at which the cells are expected to occur in a patient, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the identifying agent of Allan, et al for the identifying agent of Hou, et al in the method of Hou, et al to deliver the agent to a patient to successfully localize premalignant or malignant tissue within the patient's breast ductal network without the undue risk of retention of the radioactively labeled identifying agent in tissues where the cells are not expected to be found.

In response to Applicants' argument that "the steps needed to prepare the agent disclosed in Allan's method contradict the method set forth in Hou", the rejection states, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the identifying agent of Allan, et al for the identifying agent of Hou, et al in the method of Hou, et al to deliver the agent to a patient, because the identifying agent of Allan, et al is coupled to a targeting molecule that enables the identifying agent to specifically target malignant breast cancer cells and because the method of Hou, et al enables one to deliver the agent directly to the targeted site at which the cells are expected to occur in a patient without undue risk of retention of the identifying agent in tissues where the cells are not expected to be found. It is immaterial that the individual methods of Hou, et al and Allan, et al are different, because the rejection states that derivation of the invention would have been obvious over the combination; and the only steps needed to perform the claimed invention are those steps that are recited in the claims.

In summary, Applicants' arguments have been carefully considered but not found persuasive. Therefore, the rejection of claims 1-16 under 35 USC § 103(a) for the reason stated in section 11 of the previous Office Action is maintained.

13. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,168,779 A in view of Allan, et *al (British Journal of Cancer* **67**: 706-712, 1993), as evidenced by Krag, et al (*New England Journal of Medicine* **339**: 941-946, 1998; Form PTO-1449 (Paper

No. 7), citation AT), as evidenced by the internet contents of oncologychannel.com © 1998, 1999, 2000, 2001 for the reason stated in section 12 of the Office Action mailed March 9, 2001.

In response to the Office Action mailed March 9, 2001, Applicants traverse this rejection of the claims under 35 USC § 103(a) arguing:

(1) Barsky, i.e., US Patent No. 6,168,779 A, does not disclose elements of the claimed invention.

(2) The very broad interpretation of the patent's disclosure set forth in the Office Action cannot be sustained when the patent is taken as whole.

(3) Allan, i.e., Allan, et al, do not disclose that the antibody can be introduced into the patient other than systemically.

(4) Neither of the cited references provides the suggestion of providing the recited targeting molecule and identifying agent or cancer specific agent into the breast by intraductal introduction.

(5) One would not have been motivated to derive the claimed invention by modifying the method of Barsky in view of Allan; and no teachings exist in either reference that would have lead one of ordinary skill in the art to do so.

In response to Applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In reply to Applicants' argument that broad interpretation of the patent's disclosure cannot be sustained when the patent is taken as whole, it is supposed that Applicants are contending that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning. However, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Additionally, considering that the patent discloses, "labeled antibodies A can be used to locate and label those markers M which are near the orifice O" and provides a schematic of a method in

Figure 3, which illustrates that an orifice region of a ductal network can be identified and located "with a plurality of markers M lining the epithelium of the duct and extending to the perimeter of the orifice", it does not take much imagination to visualize a method such as that of the present claims, especially in view of the teachings of Allan, et al.

In response to Applicants' argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one would have been motivated to substitute the identifying agent of Allan, et al in the method of US 6,168,779 A because the increased specificity of the method would enable the clinician to make more accurate identification of the location of malignant breast cancer cells within the duct of a patient's breast and a more accurate determination of lymph node involvement in the patient.

In reply to Applicants' argument that no teachings exist in either reference that would have lead one of ordinary skill in the art to derive the claimed invention by modifying the method of Barsky in view of Allan, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

In reply to Applicants' assertion that the Internet contents of the oncologychannel.com, which was used as evidence in the rejection, cannot be used in the rejection because the information was down-loaded in March 2001 and is therefore not prior art, the Internet contents of the oncologychannel.com was cited as the equivalent of a general text book teaching to demonstrate that it was common knowledge in the art at the time the invention was made that ductal breast cancer is of breast epithelial cell origin. One of ordinary skill in the art would not have had to have access to the information on the Internet *per se,* at the time the invention was made; one of ordinary skill in the art at the time the invention was made would have known that

ductal breast cancer is of breast epithelial cell origin. Applicants have not provided a reason to doubt this assertion, so it appears that Applicants agree that it was common knowledge at the time the invention was made.

In summary, Applicants' arguments have been carefully considered but not found persuasive. Therefore, the rejection of claims 1-16 under 35 USC § 103(a) for the reason stated in section 12 of the previous Office Action is maintained.

***New Claim Rejections***

***Claims Rejections – 35 USC § 112, first paragraph***

14. Claims 5-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Currently claim 5 recites the term "cancer cell specific identifying agent". However, it appears that the specification lacks proper antecedent basis for recitation of this term in the claim. Because this term is not supported by disclosure in the specification, the inclusion of the term in the claim violates the written description requirement of 35 USC § 112, first paragraph. This rejection might be overcome if Applicants were to point out particular disclosures in the specification that are believed to provide proper antecedent basis for recitation of the term in the claim.

***Claim Rejections – 35 USC § 112, second paragraph***

15. Claims 9-16 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which Applicant(s) regard as their invention. Evidence that claims 9-16 fail(s) to correspond in scope with that which Applicant(s) regard as the invention can be found in Paper No. 16 filed December 4, 2001. In that paper, Applicants have stated "[t]he present invention relates to **in vivo** determinations of the presence of cancerous or precancerous cells by identifying only the location of a cancerous or precancerous cell and, if present, the location of a lesion" (page 4, paragraph 2). Applicants further state, "the methods according to the present invention do not identify the remainder of the breast duct or the sentinel lymph nodes". These

statements indicate that the invention is different from what is defined in the claim(s) because the claims are drawn to a method for determining the lymph node involvement in patients diagnosed with premalignant or malignant breast cancer growths.

***Conclusions***

16. No claims are allowed.

17. Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Applicants affirmed the election in Paper No. 8. However, claims 17-32 drawn to an invention non-elected without traverse are still pending in this application. In view of Applicants' remarks in Paper No. 16, Applicants are apparently under the impression that claims 17-32 have been canceled, but the amendment did not include a cancellation of these claims. A complete reply to this final rejection should include cancellation of non-elected claims or other appropriate action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703)

305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

DONNA WORTMAN
PRIMARY EXAMINER

slr
March 7, 2002